BJR

https://doi.org/10.1259/bjr.20190237

Received: 04 March 2019 | Revised: 23 April 2019 | Accepted: 24 April 2019

Cite this article as:
Weber DC, Lim PS, Tran S, Walser M, Bolsi A, Kliebsch U, et al. Proton therapy for brain tumours in the area of evidence-based medicine. *Br J Radiol* 2019; **92**: 20190237.

PROTON THERAPY SPECIAL FEATURE: REVIEW ARTICLE

Proton therapy for brain tumours in the area of evidence-based medicine

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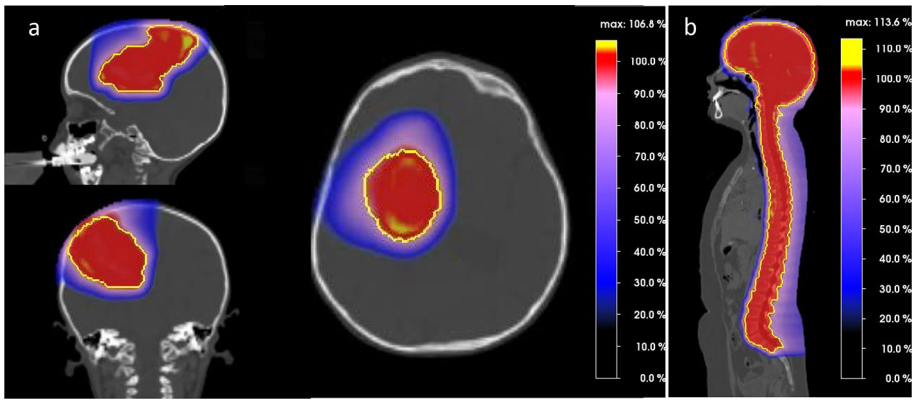
Proton therapy (PT) has been administered for many years to a number of cancers, including brain tumours. Due to their remarkable physical properties, delivering their radiation to a very precise brain volume with no exit dose, protons are particularly appropriate for these tumours. The decrease of the brain integral dose may translate with a diminution of neuro-cognitive toxicity and increase of quality of life, particularly so in children. The brain tumour patient's access to PT will be substantially increased in the future, with many new facilities being planned or currently constructed in Europe, Asia and the United States. Although approximately 150'000 patients have been treated with PT, no level I evidence has been demonstrated for this treatment. As such, it is this necessary to generate high-quality data and some new prospective trials will include protons or will be activated to compare photons to protons in a randomized design. PT comes however with an additional cost factor that may contribute to the ever-growing health's expenditure allocated to cancer management. These additional costs and financial toxicity will have to be analysed in the light of a more conformal radiation delivery, non-target brain irradiation and lack of potential for dose escalation when compared to photons. The latter is due to the radiosensitivity of organs at risk in vicinity of the brain tumour, that photons cannot spare optimally. Consequentially, radiation-induced toxicities and tumour recurrences, which are cost-intensive, may decrease with PT resulting in an optimized photon/proton financial ratio in the end.

Advances in knowledge: This review details the indication of brain tumors for proton therapy and give a list of the open prospective trials for these challenging tumors.

INTRODUCTION

Radiotherapy (RT) is an important treatment modality in the management of Central Nervous System (CNS) tumours for the optimization of tumour local control. Unlike other non-CNS malignancies, brain tumours have rarely a propensity for distant non-CNS metastases and consequentially local control is key for the cure of these challenging malignancies. Recent advances in radiation techniques include the use of intensity- (IMRT) or volumetric- modulated radiotherapy/arc therapy (VMAT), stereotactic radiosurgery/fractionated RT (SRS/SFRT) and particle therapy (mostly protons and carbon ions). As a result of optimal dose conformation provided by the latter modality, particles can be used in a dose-escalation paradigm and/or for dose sparing of critical structures/organs at risks. The former could be applied to radio-resistant CNS tumours,[1] such as skull base chordoma and chondrosarcoma, or non-benign meningiomas[2] and the latter in patients with a favorable prognosis, such as those with benign/low-grade brain tumours. For children, RT has been associated with a number of acute and late adverse events detailed later in this paper. Protons may decrease the rate of acute-[3] and, more importantly, late toxicity[4] usually seen with photon therapy and would thus increase substantially the therapeutic ratio of RT. The present paper details the most recent data for proton therapy delivered to patients with CNS tumours. Noteworthy, no data regarding carbon ions for CNS malignancies will be summarized in this manuscript and we have included skull base tumors in this brain tumor review, as it is a major indication for protons. First, this paper will detail the rational of using protons for treating brain tumors. Second, an overview of the existing trials will be described and an attempt to discuss the limitations of such studies will be made. A summary of existing data for CNS tumours

Figure 1. Sagittal, axial and coronal views of proton dose distribution for a parieto-frontal tumor. PTV is shown in yellow. Figure 1b. Sagittal view of proton dose distribution for craniospinal irradiation. PTV is shown in yellow. Noteworthy, the color wash dose level display all dose levels. As such, absence of colors equals to absence of dose.



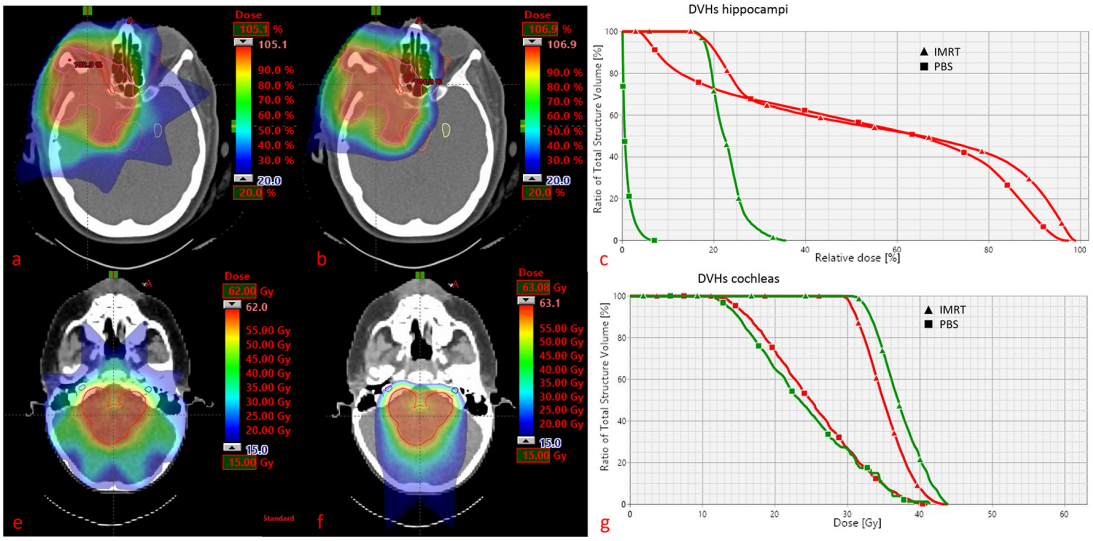
in adults and children alike will be provided and each section will finish with statements pertaining to the informed analysis. Finally, the additional costs and potential financial toxicity for patients of protons will be discussed at the end of this paper.

Proton beam therapy for brain tumours

This section elaborates on the physical rationale and dosimetric evidence for PT. Dose distribution in PT is characterized by a well-defined maximum range, which is a function of the initial energy, and a sharply defined Bragg Peak, where the bulk of the dose is deposited.[5] Beyond the Bragg Peak, the dose drops to zero within a few millimetres. Compared to photons, this dose deposition results in a superior dose conformality and lower total integral dose delivered to surrounding tissue. This remarkable dose-profile is even more pronounced for Intensity Modulated PT (IMPT) available for Pencil Beam Scanning (PBS) systems, which can achieve particularly steep dose gradients.[6] CNS tumours are inevitable in vicinity to many critical organs at risk (OARs),[7] making them an especially relevant indication for PT. This rationale is supported by clear evidence for a dose-response relationship for many radiation-induced toxicities seen after RT for brain tumours. As an example, dose to the hypothalamus and pituitary correlates with the degree of endocrine dysfunction,[8] and dose to the hippocampus correlates with memory outcomes.[9]

The dosimetric advantage of PT compared to photons is undisputed, but the magnitude of clinical benefit is unknown. This benefit may substantially differ from individual cases to cases and is to a large degree dependent on tumor location. Adeberg et al[10] evaluated the relative benefit of protons for five typical brain tumor locations and suggested that in general parietal tumours seem to benefit the most in terms of brain sparing. An exemplary

Figure 2. Supratentorial meningioma case. Doses as % of the prescribed dose and minimum dose level set at 20%. (a) IMRT dose distribution; (b) PBS dose distribution; (c) DVHs for homolateral (red) and controlateral (green) hippocampus. VOIs represented are PTV, brainstem, optic nerves and contralateral hippocampus. Infratentorial ependymoma case. Doses as absolute (GyRBE), minimum dose level set at 15GyRBE. (e) IMRT dose distribution; (f) PBS dose distribution; (g) DVHs for both cochleas (red and green). VOIs represented are PTV and both cochleas.



PT dose distribution for a parieto-frontal located brain tumor is shown in Figure 1a. Even for very complex target volumes (Figure 2) involving large parts of the brain, such in whole-ventricular RT for intracranial germ cell tumours, a dosimetric comparison study showed an approximately one-third reduction in integral dose to the brain, and also a better sparing of the circle of Willis with PT.[11] This may be clinically significant, as radiation dose delivered to the circle of Willis was recently proposed as the best predictor of stroke in childhood brain cancer survivors.[12] Moreover the dosimetric advantage is particularly striking for large target volumes, such in the case of craniospinal irradiation (CSI), where PT is able to completely spare OARs anterior to the vertebrae, as it is demonstrated in Figure 1b. Compared with modern photon techniques, PT obtained the lowest mean doses for OARs in CSI, with dose reductions of >10.0 Gy for parotid glands, thyroid and pancreas.[13] Figure 2 details the decrease of dose delivered with PT as opposed to IMRT to the hippocampus and cochleas' for a supra- and infratentorial tumor, respectively. Tamura et al[14] estimated by *in silico* modelling that the use of PT instead of photons may result in a decrease in the lifetime attributable risk of radiation-induced secondary cancer after CSI. Although these results of *in silico* modelling have been confirmed by a previous study,[15] caution should be taken not to over interpret these data stemming from a modelling computational paradigm, which do not represent 'real-life' data. Preliminary evidence suggests that this PT dosimetric gain also translates into a clinical benefit such as, for example, reduced neuro-cognitive disability[16] and improved quality of life.[17]

The superior dose conformality of PT (Figure 2) has also however its dose-delivery hazards, in terms of increased sensitivity to range and setup uncertainties, particularly so for IMPT. Robust planning[18] and robust optimization[19] can help to mitigate these dosimetric uncertainties. Another concern is the clinically use of a constant value of 1.1 for the relative biological effectiveness (RBE) for PT planning, whereas it is well known that RBE increases with increasing linear energy transfer (LET), thus presenting the highest value in the distal fall-off.[20] Other factors, not limited but including total dose, fractional dose, biological endpoint, oxygenation and tissue or cell type (characterized normally by α/β) have an influence on RBE.[20,21] LET/RBE evaluation and LET optimization of PT plans can avoid high LET areas, and therefore unintended increase in biological dose, in critical structures such as the brainstem[22] or periventricular area[23] where the brain stem-cells are located. There is a concern within the community that high-LET values at the distal range of the beam may cause toxicities be it radiological[24] or clinical.[25] For example, adjusting treatment field angles for posterior fossa tumours can substantially reduce LET values in this OAR.[26] Future developments in these and other areas are likely to only enhance the benefits of PT even further.

Establishing the role of proton therapy for the management of brain tumours: clinical trials

In the era of evidence-base medicine (EBM), high quality of data[27] is needed to justify the additional cost factor associated with proton therapy for brain and non-CNS tumours alike. Although some authors have challenged the hierarchal evidence paradigm in EBM,[28] it remains that randomised controlled trials (RCTs), representing the so-called level I evidence, are of paramount importance in the assessment of the 'value' of any treatment modality in cancer care. The ethical issues of such RCTs for proton therapy have been long debated and are not the focus of this section.[29] Clinical validation of proton therapy can also be achieved with a non-RCT paradigm: specifically, a model-based driven validation approach, with an enrichment of the experimental arm.[30] It is foreseeable that a combination of these trial strategies will best generate data that will create scientifically sound evidence on how best to select patients for protons and increase the therapeutic balance of a number of malignancies, including CNS tumours for value-based cancer management. Caution however should be stressed that, depending on the selected study endpoint, such as late toxicity including but not limited to radiation-induced tumours, the event can be observed after a long interval after PT. As such, the follow-up time of studies should be consequentially sufficient, which creates a significant challenges for prospective trials, one of which is the trial funding that should be appropriate to fund an extended period of follow-up.

A number of RCTs and prospective Phase II trials have been proposed and are currently accruing patients worldwide. Exclusion criteria of the majority of trials are previous radiation to the head and neck or brain and very extensive lesions, which would have been previously defined as gliomatosis cerebri. Several databases were queried (clinicaltrials.gov, CTSU/NRG, EORTC, PTCOG) and 43 prospective brain tumour trials activated between 1996 and 2019 were identified. Trials that assessed the value of targeted agent/immune checkpoint inhibitors or hypoxic target agents with RT including protons were excluded. Median accrual target of these trials was 80 patients, ranging from 12 to 625. Only a minority (n = 3; 7%) of trials had no age limit. Most trials were for adults (n = 23; 53%) or pediatric (n = 12; 30%) patients. Three (7%) studies were for children and adolescent and young adults. Interestingly, a substantial number of studies (n = 9; 21%) were for all brain tumours. The most common brain tumours for these trials were chordoma or chondrosarcoma (n = 7; 16%), meningioma (n = 6; 14%) and low-grade glioma (n = 6; 14%). Most of the studies were however not accruing (n = 17; 39%) or were in the process of activation (n = 2; 5%). Five (12%) studies were closed and 3 (7%) had an unknown status. The 16 (37%) remaining studies accruing patients in Europe and in the United States are detailed in Table 1. One of the low-grade glioma trials has been recently closed, achieving target-accrual. Noteworthy, WHO grade II glioma patients could be included in this trial from Boston, providing that progressive/recurrent disease was observed, neurological symptoms were uncontrolled and/or patient was aged >40 years or presented MIB-1 of ≥3%. Mean age of this cohort was 37.5 years (range, 22–56) and the gender male/female ratio was 1.9. 40% of the cohort have been followed at 5 year. The results will be published soon.

Table 1 displays also a number of tumour registries that are active in the United States, one of which is dedicated to children only. The target of total number of patient's registration is over 28'000. In Europe, it is also foreseen to have a prospective data collection

Table 1. Prospective trials and tumor registries currently accruing patients in Europe and in the United States for brain tumours

Tumor type	NCT number	Allocation	Activation (closed) [year]	# of patients	Age limit	Hypothesis	Primary endpoint	Total dose (dose per fx) [GyRBE]	status
Europe (lead)									
All brain tumorsa (*Dresden, D*)	02824731	Non-randomized Phase II	1997	418	no	rate of chronic 1 year toxicity: 15% lower with protons	Chronic toxicity @ 1 year and QoL	54-60(27-30)	accruing
WHO grade II/ WHO grade III and IDH mutated (*Essen, D*)	DRKS 00015160 NOA-25	prospective, randomized (Photons *vs* Protons)	2019	80	≥18 years	Less impairment of neurocognition after proton therapy when compared to photon radiotherapy	Neurocognition after 3 years	WHO II: 54 Gy (30 × 1,8 Gy) WHO III: 60 Gy (30 × 2 Gy) or 59,4 Gy (33 × 1,8 Gy)	accruing
United States (lead)									
All brain tumors *Washington Uni. School of Medicine*	02559752	Non-randomized Phase II	2015	80	4–21 years	Testing as measured by an acceptance rate of 60% of eligible patients administered PT	Feasibility of obtaining serial computer-based neurocognitive testing for patients administered PT	NR	accruing
Craniopharyngioma *St Judes Children Hospital*	02792582	Non-randomized Phase II	1996	140	≤21 years	Increase of PFS @ 3 years compared to photon data	PFS @ 3 years	54 (1.8)	accruing
Meningioma (Recurrent) *Washington Uni. School of Medicine*	03267836	Phase Ib	2018	12	≥18 years	Proof of concept to demonstrate on-target effect of the PT-ICI	Immunogenicity as measured by changes of CD8+/ CD4 + TILs	20(5) with concomitant Avelumab	accruing
Meningioma (non-benign) *Mass. General Hospital*	02693990	Non-randomized Phase I/II	2016	60	≥18 years	Dose escalation	Assess Safety and Utility of Increased Dose IMPT (DLT)	Dose escalation 3 × 3 design	accruing
Low-grade brain tumours *Mass. General Hospital*	03286335	Observational study	2018	100	≥18 years	None (observational)	Tumor control @ 2 years	NR	accruing
Vestibular Schwannoma *Mass. General Hospital*	01199978	Observational study	2010	30	≥18 years	None (observational)	Incidence of late toxicity @ 2 year	54(27)	Accruing

(Continued)

Table 1 (Continued)

Tumor type	NCT number	Allocation	Activation (closed) [year]	# of patients	Age limit	Hypothesis	Primary endpoint	Total dose (dose per fx) [GyRBE]	status
All brain tumours requiring CSA *Mass. General Hospital*	03281889	Feasibility	2018	20	3–18 years	To assess if IMPT is feasible for CSA vertebral body sparing	Rate of G3/4 haematological toxicity < 5% within 3 months	NR	Accruing
Recurrent Ependymoma *St Judes Children Hospital*	02125786	Non-Randomised Phase II	2014	99	1–21 years	To assess if surgery and fractionated re-irradiation with either proton or photon is effective and safe	PFS and OS @ 3 years	NR	Accruing
Glioblastoma *NRG Oncology*	02179086	Randomised Phase II	2014	606	≥18 years	Dose escalation with IMRT or PT is better than standard dose photon radiation therapy	OS dose escalation *vs* standard dose	NR	Accruing
IDH mutant Glioma (GII/III) *NRG Oncology*	03180502	Randomised Phase II	2017	120	≥18 years	PT will preserve cognition compared with IMRT	Change in cognition (CTB COMP scoreb) up to 10 years	NR	Accruing
Medulloblastoma *St Judes Children Hospital*	01878617	Phase II	2013	625	3–39 years	Assess clinical and molecular risk directed therapy	PFS @ 2 years, neurocognition @ baseline and 12 weeks	NR	Accruing
Brain tumours *Mayo*	03055364	Observational study	2017	160	≥4 years	None (observational)	Cognitive performance change (CogState) within 12 months of radiotherapy	NR	Accruing
Meningioma (G II) *NRG Oncology*	03180268	Randomised Phase III	2017	148	≥18 years	Observation *vs* adjuvant RT in the completely resected setting	PFS up to 10 years	59.4 (1.8)	Accruing
Leptomeningeal metastases *MSKCC*	03520504	Phase I	2018	26	≥10 years	Identification of safe and effective dose for PT in leptomeningeal metastases	Number of patients with DLT	30 (3) or 25 (2.5) CSA	Accruing
Patient Registries									

(Continued)

Table 1 (Continued)

Tum°r type	NCT number	All°cation	Activati°n (cl°sed) [year]	# °f patients	Age limit	Hyp°thesis	Primary endp°int	T°tal dose (d°se per fx) [GyRBE]	status
All tum°urs *Washingt°n U*	02040467	°bservational (patient registry)	2013	3200	n°	N°ne (observational)	All treatment data	NR	Accruing
All Paediatric tum°urs *Paediatric C°nsortium Registry (PCCR)*	01696721	°bservational (national patient registry)	2012	5000	≤21 years	N°ne (observational)	Establish registry	NR	Accruing
All tum°urs *Pr°ton Collaborative Group*	01255748	°bservational (patient registry)	2010	20,000	All	N°ne (observational)	Establish registry and track °utcomes	NR	Accruing

CSA, Craniospinal axis; DLT, dose-limiting toxicity; IMPT, intensity-modulated proton therapy; IMRT, intensity-modulated photon radiotherapy; NCT: NCI/Clinical Trials.NR, not reported; OS, Overall Survival; PFS, progression-free survival; QoL, quality of life; RT, radiotherapy; TIL, tumour infiltrating lymphocytes; fx, proton therapy dose per fraction.

[a]Upfront radiotherapy or re-irradition 30 Gy/RBE in 5 Gy RBE per fraction or 36 Gy/RBE in 2 Gy RBE per fraction.

[b]Clinical Trial Battery Composite score (calculated from the Hopkins Verbal Learning Test Revised [HVLT-R]) Total Recall, HVLT-R Delayed Recall, HVLT-R Delayed Recognition, Controlled Oral Word Association (COWA) test, Trail Making Test (TMT) part A and part B.

of patients treated with protons in the framework of PARTICLE-*Care*. This project is a joint collaboration of the European Organisation for the Research and Treatment of Cancer (protocol: E^{2}RADIatE, EORTC 1811) and the European Society for Radiotherapy and Oncology. It is foreseen that the first patient will be included into this prospective database by the end of 2019.

Adult brain tumours

Patient with benign brain tumours and low-grade CNS tumours might show some clinical benefit from PT. A substantial number of Low Grade Glioma (LGG) patients are long-term survivors.[31] The negative impact of photon radiation therapy on cognition has been demonstrated.[32] Plan comparative studies have shown the potential of proton therapy to decrease radiation dose delivered to OARs.[33] Currently, there are no published data of randomized trials comparing protons with photons for these tumours (Table 1). Reported results however regarding long-term toxicities from clinical proton studies show encouraging results,[34–36] although the patient numbers are small. More elucidation on the real benefit regarding the use of protons in treating LGGs can be expected from the results from the ongoing randomized trial.

Due to the poor prognosis of high-grade gliomas, a dose escalation paradigm has been advocated for these challenging tumours. A study applying an escalated boost with protons to a total dose up to 90 Gy(RBE) lead to improvement in tumor control rate as well as median survival time.[37] Nevertheless, the study enclosed only a small number of patients with no molecular analysis and a substantial number of patients had to undergo surgery due to radiation brain necrosis.

Some of the meningiomas can also be considered low-grade benign tumours. Total surgical resection is the treatment of choice for symptomatic/progressive meningioma. However, not all meningioma are suitable for surgery and therefore radiation therapy is often indicated. In particular, patients with residual non-benign, recurrent or high-grade tumours are candidates for radiation therapy. Large and complex shaped meningioma located close to brainstem (Figure 2), optical nerve, pituitary gland and cochlea may present however a therapeutic challenge and proton may provide dose escalation possibilities for non-benign meningiomas.[2] Eight retrospective studies delivering PT were conducted across a number of countries including Switzerland, Germany, Sweden and USA.[38–45] The sample size within the studies ranged from 39 to 170 participants (Table 2). Four studies included meningioma Grad 1–3,[40,42,44,45] while two included Grade 1–2[39,41] and one Grade one meningioma only.[43] In two studies a combination of photons and carbon ions was given to patients with Grade 2–3 meningioma whereas patients with Grad one tumours received proton therapy only.[42,45] Five-year local control rates for low-risk meningioma were better (94–100%) when compared with high-risk meningioma (49–88%) and tumor grading was found to be of prognostic significance in univariate analysis in four studies.[39,40,44,45] Proton therapy induced toxicity was moderate with a rate of 3.6–12.8% Grade ≥ 3 late effects. The results stemming from these small PT series are in line with modern photon series and cannot prove that proton are superior to conventional radiotherapy.

Table 2. Recent proton therapy studies for meningioma in adult patients

Author [ref]	year	Tumor type	# patients	Median Dose (GyRBE) (Range)	Median FU (months) (range)	Proton Therapy only	PBS only	Outcome	Positive prognostic factors [Univariate analysis]	Toxicity
Halasz et al.[39]	2011	Menigioma WHO Grade 1–2	*n* = 50 Grade 1: *n* = 12 (24%) Grade 2: *n* = 6 (12%) Grade not known: *n* = 32 (64%)	13 (10–15.5) in one fraction	32 (6–133)	yes	Scattering (stereotactic)	**3y-LC:** 94%	WHO Grade one *vs* atypical histology (p = 0.03) Recurrent *vs* non-recurrent meningioma (p = 0.006)	**Acute** Transient facial pain 4% **Late** Seizures associated with cerebral edema 12% Panhypopituitarism 2%
Weber et al.[40]	2012	Menigioma WHO Grade 1–3	*n* = 39 (three re-irradiation)	Grade 1–2: 52.2–56 Grade 3: 60.8 (±5.3)	54.8 (6.2–146.8)	yes	yes	**5y-LC:** Grad1: 100% Grade 2–3: 49.1%	WHO Grade 1 *vs* 2/3 (p = 0.001) GTV < 21.5 vs.>=21.5 ml (p = 0.03)	CTCA **Acute:** Grade 2: 12.5% Grade 3: 0% **Late:** Grade ≥ 3: 12.8%
Slater et al.[41]	2012	Meningioma Grade 1–2	Entire cohort *n* = 72 Grade 1: *n* = 47 (65%) Grade 2: *n* = 4 (6%) Grade not known: 21 (29%)	Grade 1: 50.4–66.6 Grade 2: 54–70.2	74 (3–183)	yes	Scattering	**5y-LC** Overall: 96% Grade 1: 99% Grade 2: 50% **5y-OS** 99% (disease-specific)	No significant differences for tumor size (GTV), dose, number of surgeries and WHO Grad	optic neurologic symptoms: 4.2% brain edema: 2.8% Transient diplopia 1.4% Panhypopituitarism 4.2%
Combs et al.[42]	2013	Meningioma WHO Grade 1–3	Entire cohort *n* = 107 WHO Grade 1: 71 (66%) WHO Grad 2/3: *n* = 36 (34%)	Grade 1: 57.6 Grade 2/3: N.R.	12 (2–39)	Grade 1: PT only Grade2/3: photons/carbon ion boost	Grade 1. Yes Grade 2/3: combination of photon/carbon	**2y-LC:** Grade 1: 100% Grade 2/3: 33%	N.R.	N.R.
McDonald et al.[38]	2015	Meningioma WHO Grade 2	*n* = 22	63 (54–68.4)	39 (7–104)	yes	N.R.	**5y-LC:** 71.1%	Dose > 60 Gy *vs* =<60 Gy (RBE) (p = 0.038)	**Acute** ≥Grade III: 0% **Late** ≥Grade III: one pt.

(Continued)

Table 2 (Continued)

Author [ref]	year	Tumor type	# patients	Median Dose (GyRBE) (Range)	Median FU (months) (range)	Proton Therapy only	PBS only	Outcome	Positive prognostic factors [Univariate analysis]	Toxicity
Vlachogiannis et al.[43]	2017	Meningioma WHO Grade 1	*n* = 170	21.9 (14–46) 2–6 Gy/fx	84 (range N.R)	yes	Scattering (stereotactic)	**5y-PFS:** 93% **10y-PFS:** 85%	Multivariate analysis: Age: $p = 0.009$ Localization: middle fossa $p = 0.04$	Pituitary insuffiency: 3.5% Radiation necrosis: 2.9% Visual impairment: 2.9% Expansive tumour cyst: 0.5%
Murray et al.[44]	2018	Menigioma WHO Grad 1–3	Entire cohort: *n* = 96 Grade 1: *n* = 61 (63%) Grade 2: *n* = 33 (34.1%) Grade 3: 2 (2.1%)	Grade I: 54 (50.4–64) Grade II and II: 62 (54-68)	56.9 (range, 12–207)	Yes	Yes	**5y-LC:** Entire cohort: 86,4% Grade 1: 95.7% Grade 2/3: 68% **5y-OS:** entire cohort: 88.2% Grade 1: 92.1% Grad 2/3: 80.7%	**5y-LC** WHO Grade 1 *vs* 2/3 ($p < .001$) Timing of PT: Initial *vs* recurrent ($p = .006$) Tumor site: Skull base *vs* non-skull base ($p = 0.014$) Gender: Female *vs* Male ($p = 0.32$) **5y-OS**	CTCA **Acute** ≥Grade III: 0.96% **Late** ≥Grade III overall: 10% optic toxicity: 6.7% brain edema: 0.96% brain necrosis: 1.9%
El Shafie et al.[45]	2018	Meningioma WHO Grade 1–3	Entire cohort: *n* = 110 Grade 1: 60 Grade 2: 7 Grade 3: 1 not known:42	Protons: 54 (50-60); 1.8–2.0/fx Carbon ion: 18; 3.0/fx	46.8 (95%CI: 39,9–53.7)	Proton: *n* = 104 Photons/Carbon ion: *n* = 6	Yes Grade 2/3: combination of photon/carbon	**5y-PFS:** Entire cohort: 96.6% Low risk: 96.6% High risk: 75%, **5y-OS**: 96.2 %	Histology: low *vs* high risk : $p = 0.02$	CTCAE **Acute:** Grade III: 1.8% (mucositis, nausea) **Late:** Grade III:3.6% (hypopituitarism, radionecrosis)

FU, follow-up; LC, local control; NR, not reported; OS, overall survival; PBT, proton beam therapy; PFS, progression free survival; fx, fraction.

Table 3. Recent proton therapy studies for skull-base tumors (chordoma and chondrosarcoma) in adult patients

Author [ref]	year	Tumor type	[a]patients	Mean Dose (GyRBE) (Range)	Mean FU (months)	Proton Therapy only	PBS only	Outcome	Positive prognostic factors LC ($p < 0.05$) [Univariate analysis]
Youn et al.[61]	2018	chordoma	34	69.6	42.8	yes	yes	5yLC: 87.3%[b] 5yOS: 92.9%[b]	Skull-base *vs* cervical
Fung et al.[53]c	2018	chordoma	106	(68.4–73.8)	61.0	no	no	5yLC: 88.6%	Tumor volume < 25 cc
Weber et al.[51]c	2018	ChSa	251	70.2	88.0	no	no	5yLC: 93.1% 5yOS: 93.6%	Tumor volume < 25 cc Non-OA compression
Takagi et al.[54]	2018	chordoma	11	65.0/20 fx	71.5	yes		5yLC: 85.0%[b] 5yOS: 86%[b]	Surgery before PT[b]
Demizu et al.[64]	2017	Chordoma & ChSa	68	70	52.6	yes	yes	5yLC: 71.1% 5yOS: 75.3%	Female gender
Weber et al.[51]	2016	Chordoma & ChSa	222	72.5	50.0	yes	yes	7yLC: 70.9% 7yLC: 93.6%[d] 7yOS: 81.7%[b]	Non-compression BS GTV ChSa *vs* chordoma
Hayashi et al.[62]	2016	chordoma	19	77.4–78.4[a]	61.7	yes	yes	5yLC: 75.0% 5yOS: 83.2%	NR
Feuvret et al.[65]c	2016	ChSa	159	70.2	77.0	no	no	5yLC: 96.4% 5yOS: 94.9%	Age < 40 years[e] primary disease status[e]
Deraniyagala et al.[66]	2014	chordoma	33	(77.4–79.4)	21.0	yes	no	2yLC: 86.0% 2yOS: 92.0%	NR
Yasuda et al.[67]c	2012	chordoma	17	68.9	46.1	no	no	5yLC: 70.0%[b] 5yOS: 83.4%[b]	≥47 years Skull-base *vs* CCJ
Fuji et al.[68]	2011	Chordoma & ChSa	16	63.0	42.0	yes	yes	3yLC: 86.0% (chordoma) 3yOS: 100.0% (chordoma) 3yLC: 100.0% (ChSa) 3yOS: 100.0% (ChSa)	NR
Noel et al.[69]	2001	Chordoma & ChSa	45	67.0	30.5	no	no	3yLC: 83.1% (chordoma) 3yOS: 91.0% (chordoma) 3yLC: 90.0% (ChSa) 3yOS: 90.0% (ChSa)	<55 years Tumor volume < 29 cc
Hug et al.[52]	1999	Chordoma & ChSa	58	70.7	33.0	yes	no	5yLC: 54.0%(chordoma) 5yOS: 88.0%(ChSa)	Tumor volume < 25 cc Non-compression BS
Terahara et al.[70]c	1999	Chordoma	115	68.9	NR	no	no	5yLC: 79.0% (chordoma) 5yOS: 59.0% (chordoma) 5yLC: 94.0% (ChSa) 5yOS: NR (ChSa)	Male gender Minimum dose Target dose EUD

(Continued)

Table 3 (Continued)

Author [ref]	year	Tumor type	[a]patients	Mean Dose (GyRBE) (Range)	Mean FU (months)	Proton Therapy only	PBS only	Outcome	Positive prognostic factors LC ($p < 0.05$) [Univariate analysis]
Munzenrider et al.[71]	1999	Chordoma & ChSa	621	(66.0–83.0)	41[d]	no	no	10LC: 54.0% (chordoma) 10OS: 54.0% (chordoma) 10yLC: 88.0% (ChSa) 10yOS: 90.0% (ChSa)	Male gender Tumor volume < 70 cc
Austin-Seymour et al.[72]	1989	ChSa	68	69.0	41	no	no	5yLC: 82% 5yDFS: 76%	NR
Berson et al.[73]	1988	Chordoma & ChSa	45	(59.4–80.0)	33pts > 1 year	no	no	5yLC: 59.0%[b] 5yOS: 62.0%[b]	ChSa Tumor volume <20 cc Non-recurrent tumour

LC, local control; OS, overall survival; ChSa, chondrosarcoma; BS, brainstem; GTV, Gross tumor volume; CCJ, cranio-cervical junction; EUD, equivalent uniform dose; PT, proton therapy; fx, fraction; NR, not reported; OA, optic apparatus; pts, patients; FU, follow-up.

[a]Hyperfractionated proton therapy

[b]Entire cohort, including skull base and extra cranial tumours

[c]Partial publication of cohort outcome in another paper

[d]Chondrosarcoma only

[e]For Progression-free survival

[f]Median value

In summary, it is unlikely that proton therapy delivered for high-grade brain tumors might translate into a substantial clinical benefit for CNS-tumor patients. Protons could however be administered to low-grade (*i.e.* glioma) or benign (*i.e.* meningioma) brain tumors, as these patients experience substantial long survival times, in order to possibly decrease the probability of long term toxicity. Alternatively, proton therapy could be administered to patients with non-benign meningioma with a dose-escalation paradigm.

SKULL-BASE TUMOURS

Skull-base chondrosarcoma (sbChS) and chordoma (sbC) are very rare tumours with an incidence of <1 per million.[46] They are usually in direct vicinity of OARs, including but not limited to the optic apparatus, brainstem, pituitary gland and cochleae and are considered radio-resistant.[47,48] Local tumour control is associated with overall survival and is thus of paramount importance.[49,50] SbChS and sbC are usually managed with cytoreductive surgery and postoperative radiotherapy. The importance of optimal surgery (*i.e.* optimizing the tumor geometry/debulking) with potentially sequential surgical procedures, before radiotherapy has been advocated by many groups.[50–54] The outcome of patients with sbChS/sbC treated with adjuvant or salvaged photon radiation therapy is not optimal. When gauging the benefit of protons for these skull-base tumours, it is important to acknowledge that, due to the rarity of this condition, only observational studies stemming usually from one institution, with few exceptions,[50] have been published. Consequentially, no level I or II evidence have been proven on the superiority of protons over photon radiotherapy, although the outcome data published by non-particle radiotherapy is somewhat poor. Two photon series reporting on 17 and 48 sbC and extra cranial chordomas patients have shown that delivering a median dose of 50 Gy with conventional radiotherapy resulted in a 5 year PFS and 5 year LC of 17 and 23%, respectively.[55,56] As such, conventional radiotherapy may provide valuable palliation for these challenging patients but chordomas are rarely cured with this therapeutic modality. It has been claimed that historical photon series, such as those reported above, do not reflect the accurate efficiency of modern photon radiotherapy series. A recent study from the UCLA group reported on 57 sbC patients treated with a median dose of 17.8 and 63.4 Gy delivered with SRS and SFRT, respectively.[57] The observed 5 year PFS for the entire cohort was only 35.2%. Of note, SRS and SFRT produced comparable rates of tumour control. Numerous modern SRS and SFRT series have shown suboptimal outcomes for sbC patients treated with these radiation modalities.[57–59] These suboptimal results may be best explained by the stereotactic margins defined during the planning process and radiation dose delivered to these patients. Regarding the former, Snider et al have shown undisputedly the importance of margins for extracranial chordomas.[60] The seminal paper by Pearlman et al have shown a dose-response for chordomas.[47] More recently, a South Korean study reported on 35 sbC patients treated with a median 75.5 EQD2 delivered by proton therapy. The observed 5 year local tumour control was 92.8 and 63.0% for patients treated with ≥69.6 and<69.6 Gy, respectively.[61] Likewise, an analysis of 863 chordoma patients captured in the National Cancer Data base has shown undisputedly that dose for chordoma was associated with a significant increase in OS on univariate analysis.[1] Other proton series have shown such a dose-response with sbC.[62] This dose-response relationship has also been observed with photons[55,63] : in the above-referred US series, higher dose of SFRT was associated with a significant higher rate ($p = 0.013$) of tumour local control.[57] As such, high-dose radiation therapy, with non-stereotactic margins, have to be delivered to chordoma patients postoperatively. Table 3 details the outcome and prognostic factors of sbChS and sbC adult patients treated with proton therapy, mostly delivered with a passive scattering paradigm. Noteworthy, the prognostic impact of gender is unproven, as all but two series with contradictory results,[64,70] have shown that chordoma is gender-neutral. Tumour volume before proton therapy, with various cut-offs ranging from 20 to 70 cc, is a major prognosticator. Interestingly, the outcome of sbC and scChSa patients have improved substantially in recent years (Table 3). Finally, delivering high dose proton radiation to the skull base tumours may induce toxicity,[52,65–69,71–74] including but not limited to the brainstem. At the Paul Scherrer Institute, we have seen no brainstem radiation toxicity in adult skull-base tumour patients treated with protons. Debus et al reported on 367 skull base tumours patients treated in Boston with combined proton/photon radiotherapy.[49] Brainstem toxicity was observed in 4.6% of cases and the estimated toxicity-free survival was 88%.

Protons should thus be the standard of care for sbC or sbChSa, as a dose escalation can be achieved with this treatment modality, maximizing the chances of cure for these challenging patients.

Pediatric brain tumours

Cancer affects more than 380'000 children aged 0–19 every year globally[75] and is the leading cause of childhood death by disease in high-income countries (HIC). Nevertheless, cancer cure rates in HIC currently are near 80% and are on the rise thanks to new advances in medical treatments This leaves many childhood cancer survivors (CCS) with a potentially normal lifespan, during which maintaining both good health status and quality of life is of paramount importance.[76] Treatment-related toxicity brings a significant morbidity burden on CCS, most of all for patients with primary brain cancers.[77] Reasons for this are an increased sensitivity due to ongoing tissue growth and neuro-cognitive development, smaller anatomic dimensions bringing critical organs closer to treatment areas and a longer lifespan left to develop side-effects. The most significant toxicities associated with brain tumor irradiation are vascular complications such as radiation necrosis (RN) and Moya-Moya syndrome, impairment of neurocognitive development, including loss of IQ scores, visual, hearing or endocrine deficits as well as skin changes such as alopecia. In the case of CSI (Figure 1b), neck, thoracic, abdominal and pelvic organs can develop late sequelae of radiation therapy. As an example, vertebral body irradiation leads to decrease of adult height[78–80] with a reported incidence rate of 3–26%.[81] RN can result in numerous symptoms or deficits, depending on its location, such as seizures or motor impairment. Seven papers reported on RN induced by proton therapy in pediatric patients (Table 4). Sample sizes ranged between 17 and 313 patients, with ages between 19 months and 10 years. Time to RN ranged between 3 and 9 months. Median PT doses of 54 Gy

Table 4. Literature review of cerebral necrosis for proton therapy

Author [ref]	Year	Tumor type	# pts	Median Age [years]	Median Dose [GyRBE] (range)	Time to RN [months]	Toxicity	Prognostic Factors
Sabin et al.[82]	2013	EP,CPC,PNET, MB, ATRT	8/17	2.5	54	3.9	47% pseudoprogression	PT after chemotherapy
Indelicato et al.[83]	2014	EP,CF,LGG, MB,PNET,PMRh	11/313	5.9	54	3	3.8% Gr < 3@2y 2.1% Gr 3 @2y	Age < 5y; PF; V55Gy, Dmax
McGovern et al.[84]	2014	ATRT	5/31	19	Local PT 50.4 CSI 54	4	16% @2y Gr1-2	Age < 5y; intensive Cht prior PT
Gunther et al.[85]	2015	EP	72 16/37 PT 6/35 IMRT	4.4 PT 6.9 IMRT	59.4 PT 54 IMRT	3.8 PT 5.3 IMRT	43%PT 17% IMRT 3PT persistent neurological deficits	PTvsIMRT higher rate of imaging changes Age > 3 y BS
Giantsoudi et al.[86]	2016	MB	4/111	10.5	54	9	3.6%@5y 2.7%@5y (grade3+)	WPF *vs* IF
Bojaxhiu et al.[87]	2018	EP,CF,LGG, MB,PNET,other	29/171	3.3	54	5	17%RN; 11%WMLs	Cht, EP, hydrocephalus
Gentile et al.[88]	2018	MB,EP,ATRT	5/216	6.6	54	8.5	2.0%@5y (grade ≥ 2)	Dmax < 55.8 Gy,V55 ≤ 6%

GyRBE, Gray in relative biological effectiveness; ATRT, atypical teratoid rhabdoid tumor; CF, craniopharyngioma; CPC, choroid plexus carcinoma; CSI, craniospinal irradiation; Cht, chemotherapy; EP, ependymoma; IF, involved field; IMRT, intensity modulated radiation therapy; LGG, low grade glioma; MB, medulloblastoma; PF, posterior fossa; PMRh, parameningeal rhabdomyosarcoma; PNET, primitive neuroectodermal tumor; RN, radiation necrosis; WML, white matter lesion; WPF, whole posterior fossa; pts, patients.

Table 5. Recent proton therapy studies for pediatric brain tumors

Author [ref]	year	Tumor type	# pts	Median Age [years]	Median Dose [GyRBE] (range)	Median FU [months] (range)	Outcome	Late Toxicity
De Amorim Bernstein et al.[96]	2013	AT/RT	10	2.3	50.4 (50.4–55.8); three pts CSI (18–23.4)	27.3 (11.3–99.4)	LC 100%, DC 80%, OS 90%	Endocrine G2 (2pts hypothyroidism, 3pts GH deficiency)
Mc Govern et al.[84]	2014	AT/RT	31	1.6	50.4 (9–54); 14 pts CSI (23.4–36)	24 (3-53)	Median OS 34.3mo, PFS 20.8mo	five pts imaging changes interpreted as RN
Weber et al.[95]	2015	AT/RT	15	1.4	54 all patients, no CSI	33.4 (9.7–69.2)	LF 20%, DBF 27%, SF 2%. 2y OS 64.6%, 2y PFS 66%	2y tox free survival 90%. No decrease of QoL after PT
Bishop et al.[91]	2014	Craniopharyngioma	52 (21 PT)	8.9	50.4 (50.4–54)	59.6 (PT 33mo)	3y OS 96%, nodular FFS 96%, cystic FFS 76%. Same outcome for PT and IMRT	Endocrine G2 77%. No difference between PT and IMRT
MacDonald et al.[97]	2013	Ependymoma	70	3.2	55.8 (50.4–60)	46 (12–140.4)	3y LC 83%, PFS 76%, OS 95% 5y LC 77%, DC 83%	one pt hypothyroidism, two pts GH deficit, two pts hearing loss, two pts cavernoma. No drop in MI and OAS scores
Mizumoto et al.[98]	2015	Ependymoma	6	5	56.7 (50.4–61.2)	24.5 (13-44)	OS 100%, PFS 80%	one pt one-time seizure, one pt alopecia, no difficulty in daily life
Ares et al.[92]	2016	Ependymoma	50	2.6	59.4 (54–60)	43.4 (8.5–113.7)	5y LC 78%, OS 84%	38% G1/2, two pts G3 deafness, one pt G5 brainstem necrosis
Sato et al.[99]	2017	Ependymoma	79 (41 PT)	3.7	55.8 (50.4–59.4)	PT 31.2 (7.2–86.4) IMRT 58.8 (13.2–140.4)	3y OS 81% IMRT *vs* 97% PT (p = .08), PFS 60% IMRT *vs* 82% PT (p = .0307), Recurrence 55% IMRT *vs* 17% PT (p = .005)	Vascular disorder G2 + 10% (6 RN, one stroke, one cavernoma)
MacDonald et al.[93]	2011	Germ cell tumors	22	11	Total 44 (30.6–57.6) 1pt IF only seven pts WVRT 19.5–23.4 1pt WBRT 25.5 13 pts CSI 18.3–27	28 (13-97)	LC 100%, PFS 95%, OS 100%	two pts hypothyroidism, 2pts GH deficit. No new NC or auditory deficit
Hug et al.[94]	2002	Low grade glioma	27	8.7	55.2 (50.4–63)	39.6 (7.2–81.6)	LF 22%, OS 85%	Moya-Moya one pt
Greenberger et al.[78]	2014	Low grade glioma	32 (nine mix PT and photons)	11	52.2 (48.6–54)	91.2 (38.4–218.4)	6y PFS 89.7%, 8y PFS 82.8%, 8y OS 100%	Endocrine G2 > 80% at 10y (>40 GFy to pituitary and hypothalamus is RF), two pts G3 vasculopathy (Moya-Moya), age > 7y and hippocampus dose RF for NC decline, VA/VF decline four events, other visual tox nine events
Jimenez et al.[100]	2013	Medulloblastoma / supratentorial PNET	15	2.9	Total 54 (39.6–54) CSI 21.6 (18–30.6)	39 (3-102)	3y LF 7.7%, OS 85.6%	Ototoxicity nine pts (2 G3), Endocrine G2 three pts, significant height loss, NS if GH deficiency pts excluded, no loss from baseline IQ
Eaton et al.[101]	2016	Medulloblastoma	88 (45 PT)	6	Total 54–55.8 CSI 23.4 (18–27)	74.4 PT pts 84 photon pts	6y RFS 78.8% PT *vs* 76.5% photon (p = .948). 6y OS 82% PT *vs* 87.6% photon (p = .285)	NR

(Continued)

Table 5 (Continued)

Author [ref]	year	Tumor type	# pts	Median Age [years]	Median Dose [GyRBE] (range)	Median FU [months] (range)	Outcome	Late Toxicity
Yock et al.[102]	2016	Medulloblastoma	59	6.6	Total 54 CSI 23.4 (23.4–36)	84 (62.4–98.4)	3y PFS 83% 5y PFS 80%, OS 83% 7y PFS 75%, OS 81%	Ototoxicity G3 + 12% at 3y and 16% at 5y and 7y, FSIQ decline by 1.5 point/y, Endocrine deficit 27%, 55 and 63% at 3, 5 and 7y, Cataract two pts, BS injury one pt, Stroke two pt

NS, not statistically significative. WBRT, whole brain radiotherapy; AT/RT, atypical teratoid/rhabdoid tumor; CSI, craniospinal irradiation ; DBF, distant brain failure; DC, distant control; FFS, failure free survival;FSIQ, full scale intelligence quotient; FU, follow-up; G, toxicity grade;GH, growth hormone; GyRBE, Gray in relative biological effectiveness; IF, involved field;LC, local control; LF, local failure;MI, mean intelligence; NC, neurocognitive; NR, not reported; OAS, overall adaptive skills; OS, overall survival;PFS, progression free survival;RF, risk factor; RFS, recurrence free survival;RN, radiation necrosis; SF, spinal failure, PT: proton therapy;VA, visual acuity; VF, visual field; WVRT, whole ventricle radiotherapy; mo, months;pts, patients.

RBE were used across all seven studies. Grade 3–4 RN ranged between 2 and 3.6% at 5 years.[82–88] PT has demonstrated its ability to better spare uninvolved normal tissues including critical OARs compared to standard photon therapy. It has therefore become a widely accepted radiation modality for several childhood malignancies. Advantages of PT for the irradiation of brain tumours reside in a better sparing of healthy brain tissue and other OARs (Figure 2), not limited but including the cochlea, the pituitary gland, the hippocampus, the optic structures and the brainstem.[89] For the spinal cord, posterior proton field arrangements (Figure 1b) allow for an excellent sparing of all organs anterior to the vertebral bodies as described above.[90] Pediatric brain tumours, for which PT has been most commonly used, are craniopharyngiomas,[91] ependymomas (Figure 2),[92] germ cell tumours,[93] low-grade gliomas,[94] medulloblastomas and atypical teratoid/rhabdoid tumours (ATRT)[95,96] (Table 5). Four retrospective studies, published with exclusively ependymoma patients, reported OS and PFS rates ranging from 84–100% to 76–80%.[92,97–99] In medulloblastoma studies,[100,102,103] sample sizes ranged between 15 and 59 patients, with ages between 2.9 and 6.6 years. The context of re-irradiation also makes a particularly strong case for the use of very conformal RT modalities such as PT, as treatment of recurrences can still lead to cure in some instances, such as for localized ependymoma relapses.[101]

The administration of protons to children with brain tumors represent an unique opportunity to decrease the likelihood of late CNS toxicity by decreasing the integral dose to the brain, especially so in very young patients with tumors such as ATRTs, ependymomas or medulloblastomas.

Costs considerations/financial toxicity

Across HICs, cancer management costs are escalating, driven mainly by consumerism in health care, the demographic transition of a growing elderly population and by the delivery of costly new therapies. Although there is an association between high-spending health care systems and lower cancer mortality,[104] it is questionable if the growth in cancer spending is sustainable in the long-time in high-income countries.

Proton therapy is an expensive anti cancer treatment, with a cost factor of approximately 2.5, when compared to modern RT techniques.[105] This is certainly due to the considerable investment costs but also due to the high operation and maintenance costs. Ongoing technical developments may lead to cost reduction but it is not expected that a dramatic decrease in costs will be reached in the near future.[106] As a result, there is an ongoing debate on the value of proton therapy and its cost-effectiveness (CE).[107,108]

As care for medical conditions, such as cancer, usually involves multiple disciplines and numerous interventions at different timepoints, the true value cannot be determined by simply comparing costs of two treatment modalities. Consequently, CE analysis must also consider patient`s longtime outcome, toxicity and quality of life by tracking patient outcomes and costs longitudinally.[109]

Four publications on CE of proton therapy in brain tumours could be identified, of note all in pediatric cohorts (Table 6). All

Table 6. Cost-effectiveness studies for proton *vs* photon therapy of brain tumors

Author [ref]	year	Tumor type	Study design	Statistical Model Method	Included Parameters	Results
Lundkvist et al.[110]	2005	Pediatric medulloblastoma	Comparison PBT *vs* IMRT	Markov cohort simulation model	Risk of hearing loss, IQ loss, GHD, hypothyroidism, osteoporosis, cardiac disease, fatal and nonfatal SMN	Gain of QUALY of 0.68 per patient; Estimated cost difference (protons *vs* photons) per patient −23,646.5 EUR ICER of −34,622 EUR/QUALY →Cost effective →Cost saving
Mailhot Vega et al.[111]	2013	Pediatric medulloblastoma	Comparison of PBT *vs* photon RT	Monte Carlo simulation	Risk of GHD, hearing loss, hypothyroidism, congestive heart failure coronary artery disease, ACTH deficiency, gonadotropin deficiency, SMN, death	Gain of QUALY of 3.46; Total difference in costs (protons *vs* photons): - 32,579.1 Dollar ICER of −9,416 Dollar/QUALY →Cost effective →Cost saving
Hirano et al.[112]	2014	Pediatric medulloblastoma	Comparison of PBT *vs* IMRT	Markov cohort simulation model	Risk of hearing loss due to cochlear dose for three different QoL measures (EQ-5D, HUI3, SF-6D)	Gain of QUALY between 0.98 and 1.82 and ICER of 11,773 and 21,716 Dollar/QUALY dependent on QoL measure used →Cost effective
Mailhot Vega et al.[113]	2015	Pediatric CNS tumors	Comparison of PBT *vs* photon RT in hypothalamic dose sparing	Markov cohort simulation model	Risk of GHD	Hypothalamic proton doses between 5 and 25 Gy can be cost-effective, between 5 and 20 Gy even cost saving in some scenarios

ACTH, adrenocorticotropic hormone; GHD, growth hormone deficiency; ICER, incremental cost-effectiveness ratio; IMRT, intensity modulated radiation therapy; IQ, intelligence quotient; PBT, proton beam therapy; QoL, quality of life; QUALY, quality adjusted life years; RT, radiation therapy; SMN, secondary malignant neoplasm.

used Markov modelling[110,112,113] and Monte Carlo simulations[111] to compare proton *vs* photon therapy. All investigators have shown that proton therapy is cost-effective with regard to long-term risk of radiation side-effects. Three studies even demonstrated a cost saving effect of proton therapy.

These analyses are based on theoretical modelling concepts using assumptions, which remain questionable. Empirical comparative data establishing the clinical advantages and health economic appropriateness of proton compared to photon therapy is lacking but urgently needed. It is foreseen that costing data will be captured in the EORTC 1811 protocol/Particle*Care*.

Most insurances reimburse the costs of proton therapy for brain tumours listed in this manuscript. Nevertheless, patients may experience expenses to cover costs for housing and traveling during 6–7 weeks treatment, special food and potentially lose wages. For some patients, these out of pocket payments can cause substantial financial distress that adversely affects a patient's quality of life, treatment choice, treatment compliance, and treatment outcome.[114] Treatment related financial distress can be just as toxic as the effects of chemotherapy or radiation and was therefore defined as a treatment related financial toxicity.[115] Approximately 16% of patients undergoing proton therapy for brain tumours in Switzerland experience moderate to severe financial distress (unpublished own data). However, very limited evidence is available about the incidence of financial toxicity, its associated morbidity and its preventability in proton therapy.

CONCLUSIONS

The dose deposition advantage of PT for the treatment of brain tumours are instantly apparent when planning comparisons of proton *vs* photon are made. Evidence for PT in adult benign and low-grade tumours is however limited on retrospective analyses. The available data suggests that proton therapy achieves good local control in some high-grade tumours with acceptable toxicity and that the toxicity profile for low-grade tumours warrants prospective analyses. For skull-base, radio-resistant tumours, high-dose (*i.e.* >70 GyRBE) proton therapy, with non-stereotactic margins, have to be delivered to patients postoperatively. Delivering protons to children with brain tumours may increase the therapeutic ratio. In the era of EBM, high-quality data needs to be rapidly generated to justify the higher costing of this radiation modality, which can have substantial financial toxicity to the patients and their families.

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